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Published

With international search report.

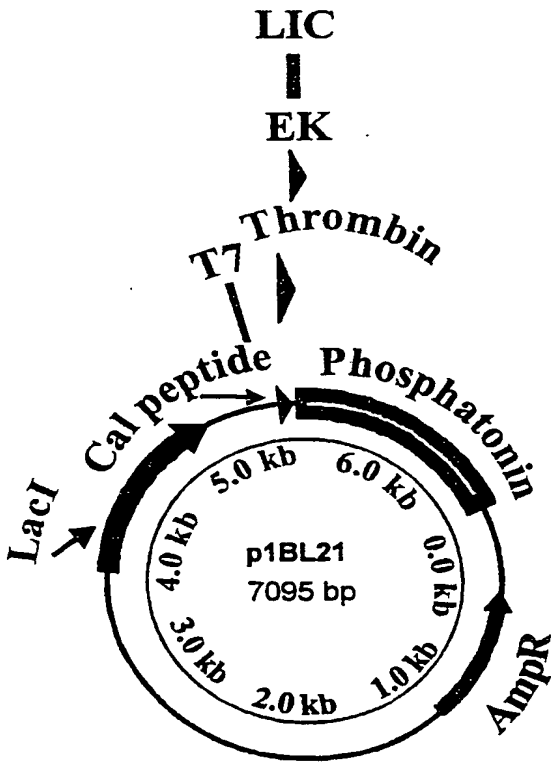
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
9 March 2000 (09.03.00)

(54) Title: HUMAN TUMOUR-DERIVED POLYPEPTIDE HORMONE PHOSPHATONIN

(57) Abstract

The present invention relates to a novel human protein called phosphatonin, and isolated polynucleotides encoding this protein. Also provided are vectors, host cells, antibodies, and recombinant methods for producing this human protein. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to this novel human protein.



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INTERNATIONAL SEARCH REPORT

Internation. pplication No
PCT/EP 99/03403

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/16 C07K14/575 A61K38/22 G01N33/68 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROWE P S N ET AL.: "Candidate 56 and 58 kDa protein(s) responsible for mediating the renal defects in oncogenic hypophosphatemic osteomalacia" BONE, vol. 18, no. 2, February 1996 (1996-02), pages 159-169, XP000856897 cited in the application the whole document ---	1-4,6,7, 14-20, 26-28,31
X	WO 95 14772 A (MATSUBARA KENICHI ;OKUBO KOUSAKU (JP)) 1 June 1995 (1995-06-01) see SEQ ID NO: 4634 (page 1417) abstract; claims 1-6 & EP 0 679 716 A (MATSUBARA KENICHI; OKUBO KOUSAKU (JP)) 2 November 1995 (1995-11-02) see SEQ ID NO: 4634 (page 1391) abstract; claims 1-6 ---	8-13,21, 31-33
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1999	11. 01. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Oderwald, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROWE P S N: "The PEX gene: its role in X-linked rickets, osteomalacia, and bone mineral metabolism" EXPERIMENTAL NEPHROLOGY, vol. 5, 1997, pages 355-363, XP000862824 cited in the application the whole document ---	40
A	LINDE A AND GOLDBERG M: "Dentinogenesis" CRITICAL REVIEWS IN ORAL BIOLOGY AND MEDICINE., vol. 4, no. 5, 1993, pages 679-728, XP000862825 ISSN: 1045-4411 cited in the application the whole document -----	

INTERNATIONAL SEARCH REPORT

Internat.. .al application No.
PCT/EP 99/03403

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first heet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24 and 40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 30
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 30

Claims 30-39 refer to activators and inhibitors of the polypeptide without giving a true technical characterization. Moreover, no such compounds are defined in the application. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT).
No search can be carried out for these compounds of such purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/03403

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9514772 A	01-06-1995	AU 8116494 A	13-06-1995
		CA 2153480 A	01-06-1995
		EP 0679716 A	02-11-1995

PATENT COOPERATION TREATY

RECD 08 SEP 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
D 1583 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03403	18/05/1999	18/05/1998
International Patent Classification (IPC) or national classification and IPC C12N15/16		
Applicant UNIVERSITY COLLEGE LONDON		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/12/1999	
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pilat, D Telephone No. +49 89 2399 8668

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/03403

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-97 as originally filed

Claims, No.:

1-40 as received on 14/08/2000 with letter of 10/08/2000

Drawings, sheets:

1/17-17/17 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 21,22,23-25,29.

because:

☒ the said international application, or the said claims Nos. 23-25 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 21,22 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 29.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-12,13,14,20,23-28,30-39
	No:	Claims	1-6,15-19,40
Inventive step (IS)	Yes:	Claims	13
	No:	Claims	7-12,14,20,23-28,30-39
Industrial applicability (IA)	Yes:	Claims	1-20,26-28,30-40
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Ad Section I: Basis of the report

Reference is made to the following documents:

D1: ROWE P S N ET AL.: 'Candidate 56 and 58 kDa protein(s) responsible for mediating the renal defects in oncogenic hypophosphatemic osteomalacia' BONE, vol. 18, no. 2, February 1996 (1996-02), pages 159-169, XP000856897 cited in the application

D2: WO 95 14772 A (MATSUBARA KENICHI ;OKUBO KOUSAKU (JP)) 1 June 1995 (1995-06-01) & EP 0 679 716 A (MATSUBARA KENICHI; OKUBO KOUSAKU (JP)) 2 November 1995 (1995-11-02)

D3: ROWE P S N: 'The PEX gene: its role in X-linked rickets, osteomalacia, and bone mineral metabolism' EXPERIMENTAL NEPHROLOGY, vol. 5, 1997, pages 355-363, XP000862824 cited in the application

1. Amendments (Article 33 (3) PCT)

The new set of claims submitted with the applicant's letters on the 10th of August 2000 appears to be admissible.

Ad Section III :Non-establishment of opinion

2. Clarity and Support (Article 6 PCT)

Claims 21 and 22 refer to a regulatory sequence of a promoter. However, this regulatory sequence is not characterized by its essential features. At present this regulatory sequence is entirely undefined. Moreover, in the absence of any disclosure of such a sequence the claimed subject-matter is speculative. Thus, claims 21 and 22 lack clarity and support.

3. Industrial applicability (Article 33 (4) PCT)

For the assessment of the present claims 23-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can

also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment or in diagnostic methods, but may allow, however, claims to a known compound for first use in medical treatment or diagnostic method and the use of such a compound for the manufacture of a medicament for a new medical treatment.
Claims 23-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Ad Section V :Reasoned statement under Rule 66.2(a)(ii); citations and explanations supporting such statement

4. Novelty (Article 33 (2) PCT)

4.1 D1 describes candidate protein(s) having "phosphatonin" activity and having a MW of approximately 56 and 58 kDa and antibodies binding specifically said candidate protein(s). The molecular weights were determined on a western blot using a preoperative antiserum (see abstract and Fig. 7). In view of D1, claim 1, referring to a polypeptide having phosphatonin activity and an approximate MW of 60 kDa, and claims 2-6, 15-19 lack novelty (see also point 4.1 below)

4.2 D2 describes a polynucleotide SEQ ID N°4634 (see p.1391) having 97,5% identity over 121 bp with the claimed SEQ ID N°1. However, said fragment resides in the untranslated region and therefore does not encode a polypeptide or a fragment thereof which is capable of regulating phosphate metabolism. Thus, claims 7-12 seems novel (see also point 5.1 below)

4.3 Because the process of transforming does not provide any new features to the claimed cell lines compared to prior art cell lines and the overexpression is a relative term, any prior art use of an osteoblast or bone cell line anticipates claim 40.

5. Inventive step (Article 33 (3) PCT)

5.1 Document D1 is considered to represent the most relevant state of the art. It discloses candidate protein(s) responsible for mediating the renal defect in Oncogenic Hypophosphatemic Osteomalacia (OHO) from which the subject-matter of claim 7 differs only in that it provides the polynucleotide sequence. The problem to be solved by the present invention may therefore be regarded as to obtain the polynucleotide sequence encoding said candidate protein(s). In order to solve the problem posed, the skilled person would have used the teaching of D1 (e.g. the preoperative antiserum) and standard molecular biology techniques and consequently would had arrived at the claimed subject-matter of claim 7 (see also D1 p.167 col.2 lines 13-19). Thus, the solution proposed in this claim lacks an inventive step.

5.2 The same objection of lack of inventive step applies mutatis mutandis to the subject-matter of claims 8-12, 14, 20, 30-32 which refer to expression vectors, to compositions, to processes of producing a polypeptide.

5.3 A process for obtaining tumor-conditioned media is described in D1 (see p.161 col.1 "Tissue culture...", furthermore the step of purifying the candidate protein(s) having a phosphatonin activity using immunoaffinity techniques is also suggested (see p.167 lines col.2 13-19).
However, new claim 13 comprises an ion-exchange chromatography. Based on D1 and general knowledged, the skilled person, looking for an alternative method of D1, would not have tried to isolate phosphatonin using a process as claimed in claim 13 with a reasonable expectation of success. Thus, claim 13 seems to involve an inventive step.

5.4 Methods of treatment of medical conditions that are related to disorders of phosphate metabolism, methods of diagnosing a pathological condition, method for identifying a binding partner and use of polypeptides or polynucleotides or antibodies specifically recognizing said candidate protein(s) as a medicament are known in the art. Similarly, the polypeptide claimed in claims 1 to 6 and the polynucleotides in claim 7 are either not new or not inventive.
Moreover, the candidate protein(s) identified are known to be involved in hypophosphatemia, in particular in OHO which is linked with a bone mineral loss (osteomalacia). Consequently, a mere use of these methods and said

polypeptides is obvious in the light of the teaching of D1. Thus, claims 23-28 and 33-38 are trivial.

5.5 D1 describes candidate protein(s) that are responsible for mediating the renal defects in OHO. D3 speculates that said candidate protein(s) may be unprocessed and the result of an defective proteolytic processing mediated by PHEX (see p.359 col.2 lines 40-51 to p.360 col.1 line 8). Thus, the skilled person, looking for an composition capable of treating OHO, would have combined the polypeptide of present claim 7 and PHEX in a preparation without any inventive activity. Therefore, claim 39 lacks an inventive step.

Ad Section VIII : Certain observations on the international application.

6. Clarity (Article 6 PCT)

6.1 Claim 1 attempts to define the "polypeptide" by means of a result to be achieved, i.e. "having a phosphatonin activity", which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added. At present, it cannot be assessed whether known products in the art falls under the scope of protection of these claims or not. The addition of an approximate molecular weight does not allow a third party to reliably distinguish the claimed compound from prior art compounds. Thus, the scope of protection of these claims is vague and indefinite.

6.2 Claims 1-3 refer to a compound which is characterized by a "phosphatonin" function (whatever this means?) and a molecular weight using different experimental conditions.
It is emphasized that a claim may be characterized solely by its parameters only in exceptional cases (see PCT Guidelines C-III, 4.7a).
This wording should be allowable where the invention cannot be **adequately** defined in any other way, provided these parameters can be clearly and reliably determined. They should not be trivial or additional parameters not measured for prior art compound(s). In this context, the protein may be identified by means of its amino acid sequence. Thus, the molecular weight cannot be considered as defining sufficiently said polypeptide. Thus, claims 1-3 lack clarity. The same

objection remains valid for claims 16-18.

6.3 Claim 4 refers to an polypeptide which is "obtainable" from a particular cell line. This product cannot be distinguished from the prior art polypeptide obtained from another source, because the mere origin does not confer to said product any distinguishing feature.
The same objection and rationale applies to the wording "encodable" of claim 5.
The same objection applies to claim 15 as well.

6.4 Claim 5 refers to a "immunologically or biologically active fragment". Any fragment having a certain length and a biological activity (e.g. epitope or binding activity) falls under the scope of protection of this claim.

6.5 Claim 5c lacks clarity, since the term "derived" is vague and indefinite. The applicant should define in the claims what is understood by said term. A polypeptide having a phosphatonin activity and being "derived" by ways of mutations is not clear. It encompasses any prior art protein having a similar activity, the sequence being of no relevance.

6.6 Claim 5d refers to a polynucleotide comprising the complementary strand which to hybridize to any polynucleotide as defined in a) to c).
Since, the polynucleotide claimed in point c) and the hybridization conditions are not identified in the claim, the claimed subject-matter is indefinite (see point 6.5 above).

6.7 Claim 5e refers to a polynucleotide encoding a polypeptide sequence which has a 60% identity to a amino acid encoded by a polynucleotide defined in claims 5c), d). Since the polynucleotide of claims 5c) d) are undefined (see points 6.5 and 6.6, the amino acid encoded by these polynucleotide is undefined as well. Ultimately, the polynucleotide encoding a polypeptide which is 60% identical to a undefined polypeptide lacks clarity.

6.8 Claim 5f is unclear insofar as the polynucleotides encoding the polypeptides identified in claims 5 c)to d) are unclear. The same objection applies to item 5h)-j). Due to the wording used claim 5 c)g)h)i)j) is anticipated by prior art polypeptides.

For example, the present description states that the MEPE C-terminal region (414-427) shares 80% to a recurring motif found in DPP as well as two related sequences found in DSP at position 576-589 ad 800-813. Another sequence homology as been found which shares homology to DMA-1 at residues 408-429 (see present description p.78 and Fig.12, Table II). These proteins must be considered as derivatives or as proteins encoded by a polynucleotide which hybridizes to the C-terminal part of MEPE and as proteins which share at least one epitope bearing portion with MEPE.
In addition any prior art with an "phosphatonin activity" (whatever this means?) having an unrelated epitope bearing portion which originates from the 40% unrelated amino acid sequence of item e) or from the non-hybridizing part of the polynucleotide of item d) or the unrelated added part of item c) anticipates the claimed subject-matter.

6.9 Claim 6 refers to a polypeptide which is capable of regulating phosphate metabolism. As already objected to in point 6.2 above, the product must be adequately and unequivocally defined by these parameters and they should be sufficient to reliably distinguish the claimed compound from the prior art compounds, so that a third party may determine without any doubt for which compound protection is actually sought. The parameters employed should not be merely additional parameters which were not measured for prior art compound(s) (e.g. a functional requirement). As such claim 6 lacks clarity.

6.10 Claim 10 is obscure because the hybridizing conditions are not defined and because the subject-matter encompass product which have no function anymore. It is reminded that negative features may only be used if the subject-matter cannot be defined more clearly and concisely by means of positive features (see PCT Guidelines C-III 4.12). The same objection is applicable to claim 18.

F ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 January 2000 (07.01.00)	
International application No. PCT/EP99/03403	**Applicant's or agent's file reference** D 1583 PCT
International filing date (day/month/year) 18 May 1999 (18.05.99)	**Priority date** (day/month/year) 18 May 1998 (18.05.98)
Applicant ROWE, Peter	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

01 December 1999 (01.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
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Facsimile No.: (41-22) 740.14.35

Authorized officer

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